Sensitization of the Adrenal Cortex to Angiotensin II in Sodium-Deplete Man

By Wolfgang Oelkers, Jehoida J. Brown, Robert Fraser, Anthony F. Lever, James J. Morton, and J. Ian S. Robertson

ABSTRACT

The effect of sodium depletion on the dose-response relationships of angiotensin II to aldosterone and blood pressure was studied. Arterial plasma angiotensin II and aldosterone and arterial blood pressure were measured before and during the incremental infusion of angiotensin II into sodium-replete and sodium-deplete subjects. Sodium depletion caused a distinct steepening of the angiotensin II-aldosterone dose-response curves in four of five subjects and a concurrent diminution in the pressor effect of angiotensin II. Administration of angiotensin II did not demonstrably alter the half-life of aldosterone. Sodium depletion did not change the plasma concentrations of sodium or potassium, but it was accompanied by a significant increase in plasma levels of 11-hydroxycorticosteroids and magnesium. The contrasting effects of sodium depletion on the aldosterone and the pressor dose-response curves favored sodium retention. These results are consistent with an important role for the renin-angiotensin system in the control of aldosterone secretion in man.

KEY WORDS

aldosterone
magnesium
blood pressure
ACTH
dose-response curves

The hypothesis formulated by Gross (1, 2) and Davis (3) that the renin-angiotensin system is a regulator of aldosterone secretion has been supported by studies in man which show that the infusion of angiotensin II stimulates increases in aldosterone secretion (4), excretion (5, 6), and plasma concentration (7). Plasma renin assays have provided further support for this hypothesis, because parallel changes in renin and aldosterone have been demonstrated (8, 9) in a wide variety of physiological and pathological situations, albeit with some noteworthy exceptions. It should be emphasized, however, that such evidence is circumstantial; the possibility that the changes in renin and its active product, the octapeptide angiotensin II, are within a range capable of affecting aldosterone secretion remains to be demonstrated (8, 10).

Two recent reports (11, 12) have seriously questioned the role of the renin-angiotensin system in the control of aldosterone secretion during sodium deprivation in man. Mendelsohn et al. (12) could not find a consistent increase in plasma angiotensin II concentration or an increase in sensitivity of the adrenal cortex to angiotensin II in sodium depletion. Boyd et al. (11) similarly claimed that adrenocortical sensitivity to angiotensin was not markedly enhanced in sodium depletion. However, their results differed from those of Mendelsohn et al. (12) in that they observed fairly consistent, albeit small, elevations in basal plasma angiotensin II levels. Both groups concluded that the renin-angiotensin system was not the major factor causing the increased aldosterone secretion in sodium-deplete man.

These two studies (11, 12) are, however, open to objections. Each attempted to assess adrenocortical sensitivity by the administration of angiotensin II at a single dose rate in sodium repletion and sodium depletion. As explained elsewhere (13), it is not possible to distinguish changes in the threshold response from changes in the slope of the dose-response curve by examining the action of single doses of angiotensin II. Therefore, the effects of a series of graded doses must be assessed as conceded by Boyd et al. (11). Furthermore, Boyd et al. (11) used venous blood to measure angiotensin II during the intravenous administration of angiotensin. It has been shown (14) that, during the intravenous infusion of angiotensin II, the arterial plasma concentration of angiotensin II immu-
noreactive material differs considerably from the venous plasma concentration. Consequently, under these circumstances, venous plasma cannot validly be used to assess the concentration of angiotensin II reaching the adrenals in arterial blood.

In the study presented in this paper, the problem of renin-angiotensin involvement in aldosterone secretion induced by sodium depletion in man has been re-investigated. Angiotensin-aldosterone relationships in other species have been reviewed recently by others (15–17).

Methods

All experimental procedures were approved by the Ethical Supervisory Committee of the Western Infirmary, Glasgow. Informed consent was obtained from the participants: one male convalescing from duodenal ulceration, one female with mild lymphedema localized to one foot, and seven healthy laboratory workers were used. Their ages ranged from 26 to 40 years. The highest arterial blood pressure attained in any subject during the administration of angiotensin was 135/95 mm Hg.

Infusions of 1-Asp-NH₂-5-Val-angiotensin II (Hypertensin, Ciba) and of 1-Asp-5-Ile-angiotensin II (Division of Biological Standards, National Institute for Medical Research, London) were given; 1-Asp-5-Ile-angiotensin II was purified by passage through 0.22-μm Millipore filters.

Plasma angiotensin II concentration was measured by the method of Dusterdieck and McElwee (18). Plasma aldosterone was estimated by a modification of the double-isotope derivative technique of Fraser and James (19) or by the radioimmunoassay method of Fraser et al. (20). A close correlation has been demonstrated (20) in concurrent measurements made in the same plasma samples with these two techniques. Plasma 11-hydroxycorticosteroids were estimated by the fluorometric method of Mattingly (21); sodium and potassium concentrations in plasma and urine were estimated by flame photometry, and plasma magnesium was estimated by atomic absorption spectrophotometry (22).

Blood pressure was measured by a sphygmomanometer; data for control and infusion periods were the means of four to six measurements. Mean blood pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

Intravenous infusions and arterial and venous sampling were performed via indwelling catheters as described previously (14). All experiments were started between 8 AM and 9 AM after 8–12 hours of overnight recumbency and fasting. The subjects lay quietly throughout the studies in an isolated room, but they were not permitted to sleep.

Preliminary Experiments

Establishment of Steady Plasma Concentrations of Angiotensin II and Aldosterone during Angiotensin II Infusion.—Two males received dextrose (5%, iv) for 60 minutes followed by 1-Asp-NH₂-5-Val-angiotensin II (6 ng/kg min⁻¹) for 150 minutes. Venous blood samples were taken at 20 minutes and 5 minutes before the administration of aldosterone and at 30, 60, 90, 120, and 150 minutes after the administration of angiotensin had been started (Fig. 1).

Comparison of 5-Val- and 5-Ile-Angiotensin II.—Two males were studied on two different occasions separated by an interval of 3–4 weeks. For 4 days they were fed a fixed diet containing 147 and 152 mEq of sodium and 60 and 71 mEq of potassium daily, respectively. On the morning of the fifth day they received an infusion of 5% dextrose for 1 hour followed by the administration of angiotensin, 1-Asp-NH₂-5-Val-angiotensin II, on the first occasion and 1-Asp-5-Ile-angiotensin II on the second occasion, at incremental dose rates of 2 ng/kg min⁻¹ and 4 ng/kg min⁻¹ for 60 minutes each and 8 ng/kg min⁻¹ for 15 minutes (limitation of infusion duration at the highest dose rate was necessary because of a shortage of the 5-Ile-octapeptide). Arterial and venous blood samples were drawn at 20 minutes and 5 minutes before the administration of angiotensin and at 2–5 minutes before the end of each angiotensin infusion period. Because of the brief infusion, aldosterone was not measured at the highest dose rate.

Effect of Administration of Angiotensin on the Metabolic Clearance of Aldosterone.—In one normal male, ¹⁴C-Aldosterone (900 dpm, iv) (40 c/mM, New England Nuclear Corp.) was injected, and 10 ml of blood was withdrawn into heparin 1, 7, 12, 30, 50, and 70 minutes later from a vein in the opposite arm. 1-Asp-NH₂-5-Val-angiotensin II was then infused (6 ng/kg min⁻¹); a second dose of labeled aldosterone was given 60 minutes after the start of the infusion, and venous blood samples were subsequently withdrawn as before.
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acid (0.1N), and water and was evaporated to dryness. The residue was acetylated by incubation with acetic anhydride (0.1 ml) and pyridine (0.1 ml) at 35°C for 16 hours and, after the removal of excess reagents, 100 μg of aldosterone diacetate was added. The residue was then chromatographed according to the thin layer system and paper system no. 2 described by Fraser and James (19). The aldosterone diacetate regions of the paper chromatogram were eluted and assayed for 3H and 14C. From these data the 3H-aldosterone concentration of the plasma samples and the half-life of the hormone were calculated.

MAIN EXPERIMENT

This experiment was performed in four males and one female. Each subject received a constant diet with a sodium content of 129-150 mEq and a potassium content of 55-84 mEq daily for 3 full days; the first angiotensin infusion study was performed on the morning of the fourth day. Following the infusion of angiotensin, furosemide (30-60 mg, iv) was given, and each subject was then changed to a daily diet containing only 9-12 mEq of sodium; potassium intake was maintained at the previous level. On the morning after the third full day of low-sodium intake the angiotensin infusion was repeated.

Each infusion study included the administration of 5% dextrose for 60 minutes, followed by the administration of 1-Asp-NH$_2$-5-Val-angiotensin II at 2, 4, and 8 ng/kg min$^{-1}$ for 60 minutes each. Arterial and venous blood samples were withdrawn at 20 minutes and 5 minutes before the beginning of infusion of angiotensin and 55 minutes after the beginning of each infusion. As previously reported (14), during the infusion of angiotensin II, arterial plasma concentrations of immunoreactive material consistently exceeded venous plasma concentrations; the discrepancy increased with increasing doses. Consequently, only the arterial values were considered in the present paper.

In each infusion study, blood pressure was measured every 10 minutes beginning 40 minutes before the introduction of angiotensin.

Results

PRELIMINARY EXPERIMENTS

Establishment of Steady State of Angiotensin II and Aldosterone.—As shown in Figure 1, during hr infusion of angiotensin II at 6 ng/kg min$^{-1}$, there was no tendency for venous angiotensin II immunoreactive material to increase further after 30 minutes or for aldosterone to change systematically after 60 minutes. This effect on aldosterone confirms earlier reports (7, 11). Therefore, 60 minutes from the start of a given dose of exogenous angiotensin was chosen as a suitable sampling time or the estimation of plasma aldosterone.

Comparison of 5-Val- and 5-Ile-Angiotensin I.—In two subjects and with both forms of angiotensin II, comparable increments in arterial plasma angiotensin II produced comparable increments in mean blood pressure (Fig. 2). In both subjects, 5-Ile-angiotensin II was associated with somewhat greater increments in plasma aldosterone for a given plasma angiotensin II concentration. This aspect seems worthy of further study.

Effect of Angiotensin II Infusion on the Half-Life of Aldosterone.—The half-life of injected aldosterone was 29.7 minutes before infusion of angiotensin II and 30.3 minutes during infusion of angiotensin II. Ford et al. (23) have reported that the metabolic clearance rate of aldosterone appears to be unaffected by sodium deprivation. Therefore, it was assumed that changes in plasma aldosterone in the present study reflected changes in aldosterone secretion.

MAIN EXPERIMENT

Effect of Sodium Depletion on the Pressor and Aldosterone Responses to Angiotensin II.—Detailed results are given in Table 1. Cumulative
sodium losses (urinary output minus dietary intake) induced by furosemide and 3 days of low-sodium intake in the five subjects were 105, 247, 97, 148, and 144 mEq, respectively. Cumulative potassium balances similarly computed were -9, -103, -68, 25, and 53 mEq, respectively. There was no significant difference in the plasma concentration of sodium or potassium before and after sodium depletion: the sodium concentration was 138.54 ± 2.57 (SD) mEq/liter before depletion and 138.50 ± 1.82 mEq/liter after depletion, and the potassium concentration was 3.89 ± 0.24 mEq/liter before depletion and 3.83 ± 0.35 mEq/liter after depletion. Plasma magnesium was distinctly elevated in sodium depletion (1.94 ± 0.08 mEq/liter before depletion and 2.10 ± 0.13 mEq/liter after depletion; paired \( t = 4.16, P < 0.001 \)).

Differences of angiotensin II and aldosterone were distinguishable in subjects 1-4

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R = sodium replete, D = sodium deplete, All = angiotensin II, and 11-OHCS = 11-hydroxycorticosteroids. If no value is given the sample was lost. *For each subject the significance of the change in slope of the angiotensin II-aldosterone dose-response curve was assessed by the F-test for equality of regression slopes. Subject 1: \( F = 19.46, df = 1.6, P < 0.01 \); subject 2: \( F = 2.86, df = 1.4, NS \); subject 3: \( F = 30.71, df = 1.6, P < 0.001 \); subject 4: \( F = 11.21, df = 1.6, P < 0.025 \); subject 5: \( F = 2.85, df = 1.8, NS \)."
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Figure 3

Concurrent arterial plasma angiotensin II and plasma aldosterone concentrations before (solid circles) and after (open circles) sodium depletion in subject 3. Abscissa is a log scale. Basal samples correspond to the two lowest replete and the two lowest deplete angiotensin II values (Table 1). The difference in slope of the two curves is highly significant on F-test ($P < 0.001$). This difference was also apparent in the zone of overlap ($P < 0.05$).

In sodium repletion, the biggest increments in aldosterone were observed at angiotensin infusion rates of 2 or 4 ng/kg min$^{-1}$, with little or no additional rise in aldosterone at the highest dose (8 ng/kg min$^{-1}$) in any subject. By contrast, following sodium depletion, substantial increments in aldosterone were seen at all angiotensin infusion rates; two subjects showed the greatest increases at the highest rates of angiotensin infusion. This observation suggests, but does not establish, that the highest angiotensin and aldosterone values of sodium depletion occurred at or near the upper end of the sigmoid dose-response curves. By contrast, after sodium depletion, the highest points seen were still on the steep part of the respective curves.

Subject 5 had a very flat dose-response curve both before and after sodium depletion and showed a slightly anomalous blood pressure response.

In all five subjects, the basal plasma aldosterone concentrations were higher for the concurrent plasma angiotensin II levels after sodium depletion than those that would have been predicted from the dose-response curves of the sodium-replete state.

The pressor dose-response relationship to angiotensin II was altered differently by sodium depletion. The average mean basal blood pressure in the five subjects was $77.6 \pm 5.7$ (SD) mm Hg during sodium repletion and $78.0 \pm 5.7$ mm Hg after sodium depletion. As in previous studies, the pressor effect of infused angiotensin was diminished by sodium depletion. The relationship between the arterial plasma angiotensin II concentration and the change in mean arterial blood pressure for individual subjects is shown in Figure 4. In sodium repletion this relationship appeared to comprise the lower parts of the sigmoid dose-response curves where near-maximal responses had not been attained. The shape of these curves indicated that in such circumstances fluctuations of arterial plasma angiotensin II within the normal range of 5 to 35 pg/ml were not likely to influence the arterial blood pressure by more than 10 mm Hg via a direct pressor effect. In sodium depletion, a roughly parallel shift of the curves to the right was seen in all cases, but in subject 5 (Table 1), who had a shallow angiotensin II-aldosterone dose-response curve in sodium depletion, the pressor curve was distinctly flat.

Changes in the blood pressure and the aldosterone response threshold were less easy to interpret. The increments in arterial plasma angiotensin II necessary to produce a 5-ng/100 ml increase in plasma aldosterone ranged from 6 to 77.
Individual response curves of mean blood pressure (BP) to arterial plasma angiotensin II before (solid circles) and after (open circles) sodium depletion in the five subjects of the main experiment. Abscissa is a log scale.

Discussion

The present experiments have shown that the aldosterone and the pressor dose-response curves to arterial plasma angiotensin II infusions are modified in contrasting ways in sodium depletion in man. The magnitude of the sodium deficit in these experiments was slightly more than that observed in normal subjects after 5 days of dietary sodium deprivation (24, 25) and, thus, seemed physiologically relevant. More severe sodium deficiency is difficult to achieve by dieting because of the efficiency of renal sodium conservation.

In four of the five subjects examined, sodium depletion was accompanied by a distinct steepening of the aldosterone dose-response curve to angiotensin II. In these studies there was no evidence of a modification of aldosterone metabolic clearance by the infusion of angiotensin II; consequently, the changes in plasma aldosterone concentration probably reflected corresponding changes in the aldosterone secretion rate. No obvious systematic changes in plasma aldosterone or angiotensin II concentrations were seen after 1 hour of infusing a given dose of angiotensin. Therefore, 1 hour appeared to be an adequate time for the establishment of a steady state.

The mechanism for the sensitization of the adrenal cortex to angiotensin II remains to be determined. No significant changes in plasma potassium concentration occurred, and cumulative potassium balance was negative in three of the five subjects. The only person who did not show a clear increase in sensitivity following sodium depletion (no. 5) had a calculated positive potassium balance of 53 mEq.

Similarly, plasma sodium concentration did not change significantly in the 3 days of sodium deprivation in contrast to the distinct fall seen in normal subjects deprived of sodium for 5 days (24). This finding does not exclude the possibility that sodium deficiency acts more subtly on the adrenal cortex in the absence of detectable changes in plasma sodium or potassium concentration.

A highly significant increase in plasma magnesium concentration was observed in sodium depletion in the present experiments, but the physiological importance of this finding remains uncertain. Studies in man (26), rat (27), and dog (28, 29) have suggested that a rise in plasma magnesium probably would not stimulate aldosterone secretion. However, this possibility deserves further examination. Many protein and polypeptide hormones appear to owe their effects to a stimulation of adenylyl cyclase activity (30). Adrenocorticotropic (ACTH) (31, 32) and angiotensin II (33) are not exceptions. Magnesium ions are essential for the functioning of this cyclase system (34) and for other cyclases (35). Variations in the plasma concentrations of magnesium may therefore influence the adrenal response to ACTH and angiotensin.

The increase observed in plasma 11-hydroxycorticosteroid concentration in sodium deficiency suggested the possibility of a rise in the circulating ACTH level in this situation. The fluorometric method (21) used to estimate 11-hydroxycorticosteroids detects cortisol, corticosterone and a number of other compounds (36). Boyd et al. (11), using the same method, also found an increase in plasma 11-hydroxycorticosteroid concentration in sodium depletion; however, this increase was not evaluated statistically. In the present paper, the elevation in plasma 11-hydroxycorticosteroids in
sodium depletion relative to the level in sodium repletion was most marked under basal circumstances but became less marked during infusion of angiotensin II. In both situations a significant fall in plasma 11-hydroxycorticosteroid concentration occurred during the administration of angiotensin. However, this fall was not necessarily a consequence of the administration of angiotensin, because the experiments were conducted between 8 AM and 1 PM when an endogenous fall in plasma cortisol is usual. Rayyis and Horton (37) have reported that administration of angiotensin II in man causes a rise in circulating ACTH, although this rise is accompanied by a fall in plasma 11-hydroxycorticosteroids. This decrease in 11-hydroxycorticosteroids was estimated by a competitive protein-binding method. After suppression of ACTH by dexamethasone, angiotensin II caused only a minimal rise in aldosterone. This study (37) clearly indicates the importance of ACTH in the adrenocortical response to angiotensin II. Previous work (38) has shown that physiological increases in ACTH levels may cause a marked rise in plasma aldosterone concentration in sodium-deplete human subjects. Therefore, it is possible that ACTH released in response to angiotensin II infusion may contribute to the changes in plasma aldosterone seen in the experiments reported in this paper.

Another possibility, which has been considered by Ganong et al. (39), is that angiotensin may have a trophic effect on the adrenal cortex. According to this theory, exposure to high circulating levels of angiotensin II for several days, as occurs in sodium depletion (9, 14, 18, 24), might enhance the biosynthetic potential possibly by inducing hypertrophy of the zona glomerulosa; therefore, further increments of angiotensin II would have an increased effect on aldosterone secretion.

Finally, there remains the possibility that an unidentified hormone is responsible for the sensitization of the adrenal cortex to angiotensin II. Dale and Melby (40) have recently isolated a 16-α-hydroxy derivative of 18-hydroxy-deoxycorticosterone from human adrenal glands and, although this derivative seems unlikely to possess marked mineralocorticoid activity, it indicates the presence of unstudied pathways of steroid metabolism that may yield important hormonal compounds.

Whatever the precise mechanism for the sensitization of the adrenal cortex to angiotensin II in sodium deficiency turns out to be, the present studies indicate an important role for the renin-angiotensin system in the control of aldosterone secretion in man. As suggested previously (41, 42) the divergent effects of angiotensin II on aldosterone and blood pressure facilitate sodium conservation under these circumstances. Not investigated in this paper, but possibly of equal importance in the regulation of sodium balance, are the direct actions of angiotensin II on the kidney (43, 44).

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OELKERS, BROWN, FRASER, LEVER, MORTON, ROBERTSON


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